US-PAT-NO: 6242196
DOCUMENT-IDENTIFIER: US 6242196 B1

TITLE: Methods and pharmaceutical compositions for inhibiting tumor cell growth

DATE-ISSUED: June 5, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP	CODE	COUNTRY
Spiegelman; Bruce M.	Waban	MA	N/A		N/A
Altiok; Soner	Cambridge	MA	N/A		N/A
Mueller; Elisabetta	Boston	MA	N/A		N/A
Sarraf; Pasha	Boston	MA	N/A		N/A
Tontonoz; Peter	San Diego	CA	N/A		N/A

US-CL-CURRENT: 435/7.1; 435/18 ; 435/4 ; 548/146

ABSTRACT:

A method for inhibiting proliferation of a PPAR .gamma.-responsive hyperproliferative cell which comprises the step of contacting the cell with (I) an inhibitory amount of a PPAR.gamma. agonist and (II) a MAP kinase inhibitor is disclosed. A method for treating or prophylactically preventing in an animal subject a disorder characterized by unwanted proliferation of PPAR.gamma.-responsive hyperproliferative cells which comprises administering to the subject (I) an inhibitory amount of a PPAR.gamma. agonist and (II) a MAP kinase inhibitor is also disclosed. Pharmaceutical compositions comprising a therapeutically effective amount of a PPAR.gamma. agonist

and a MAP kinase
inhibitor are disclosed for use in the methods.

35 Claims, 36 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 24

---------- KWIC ---------

Detailed Description Text - DETX:

The subject method may involve, in addition to the use of PPAR.gamma. agonist (and optional RxR agonists and/or MAP kinase inhibitors), one or more other anti-tumor substances. Exemplary combinatorial therapies combining with PPAR.gamma. agonists include the use of such as agents as: mitotic inhibitors, such as vinblastine; alkylating agents, such as cisplatin, carboplatin and cyclophosphamide; antimetabolites, such as 5-fluorouracil, cytosine arabinoside, hydroxyurea or N-[5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-m -thenoyl]-L-glutamic acid; intercalating antibiotics, as for example adriamycin and bleomycin; enzymes, such as asparaginase; topoisomerase inhibitors, such as etoposide; biological response modifiers, e.g., to enhance anti-tumor responses, such as interferon; apoptotic agents, such as actinomycin D; and anti-hormones, for example antioestrogens such as tamoxifen or, for example antiandrogens such as 4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(t l) propionanilide. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L3	1	wo-200040268-$.did.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 17:46			0
2	BRS	L4	3	microtubule adj interfer$3 adj agent	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 17:47			0
3	BRS	L5	317	(tubulin adj polymerization) same inhibit$3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 17:48			0
4	BRS	L6	5928	(dolastatin adj "10") or tzt-1027 or vincristine or vinblastine or vindesine or maytansine or rhizoxin or phomopsin or ustiloxin or combrestatin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 17:50			0
5	BRS	L7	4	ERK-Map adj kinase	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 17:51			0
6	BRS	L8	3	7 same inhibit$3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 17:50			0
7	BRS	L9	76	pd98059 or u1026 or pd1843522	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 17:51			0
8	BRS	L10	1852	(Map adj kinase) or (Map adj kinase adj kinase) or (map adj kinase adj kinase adj kinase)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 17:52			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
9	BRS	L11	764	10 same inhibit$3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 17:53			0
10	BRS	L12	19	(4 or 5 or 6) same (8 or 9 or 11)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 18:12			0
11	BRS	L13	2	wo-9740842-$.did.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 18:14			0
12	BRS	L14	1	kohno adj michiaki.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 18:15			0
13	BRS	L15	250	watanabe adj kazushi.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 18:16			0
14	BRS	L16	1	15 and 12	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/25 18:16			0

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=> s microtubule interfering agent
L1 71 MICROTUBULE INTERFERING AGENT

=> s (tubulin polymerization) (p) inhibit?
L2 2072 (TUBULIN POLYMERIZATION) (P) INHIBIT?

=> s (dolastatin 10) or tzt-1027 orvincristine or vinblastine or vindesine or maytansine or rhizoxin or phomopsin or ustiloxin or combrestatin
L3 60255 (DOLASTATIN 10) OR TZT-1027 ORVINCRISTINE OR VINBLASTINE OR VINDESINE OR MAYTANSINE OR RHIZOXIN OR PHOMOPSIN OR USTILOXIN OR COMBRESTATIN

=> s l1 or l2 or l3
L4 61971 L1 OR L2 OR L3

=> s (erk-map kinase) or (map kinase) or (map kinase kinase) or (map kinase kinase kinase)
L5 49667 (ERK-MAP KINASE) OR (MAP KINASE) OR (MAP KINASE KINASE) OR (MAP KINASE KINASE KINASE)

=> s l5 (p) inhibit?
L6 18552 L5 (P) INHIBIT?

=> s pd98059 or u1026 or pd1843522
L7 10056 PD98059 OR U1026 OR PD1843522

=> s l6 or l7
L8 25835 L6 OR L7

=> s l4 (p) l8
L9 28 L4 (P) L8

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PROCESSING COMPLETED FOR L9
L10 11 DUPLICATE REMOVE L9 (17 DUPLICATES REMOVED)

=> d l10 1-11 ibib abs

L10 ANSWER 1 OF 11 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002677806 MEDLINE
DOCUMENT NUMBER: 22325749 PubMed ID: 12438277
TITLE: Brain-derived neurotrophic factor activation of TrkB protects neuroblastoma cells from chemotherapy-induced apoptosis via phosphatidylinositol 3'-kinase pathway.
AUTHOR: Jaboin Jerry; Kim Chong Jai; Kaplan David R; Thiele Carol J
CORPORATE SOURCE: Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland 20892, USA.
SOURCE: CANCER RESEARCH, (2002 Nov 15) 62 (22) 6756-63.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021120
Last Updated on STN: 20021218
Entered Medline: 20021217
AB Neuroblastoma (NB) tumors expressing high levels of brain-derived neurotrophic factor (BDNF) and TrkB are associated with poor 5-year survival outcomes. Our previous studies indicated that BDNF blocked the cytotoxic effects of ***vinblastine*** on NB cells. Here we evaluated the ability of BDNF to decrease the chemosensitivity of NB cells to a number of common chemotherapeutic agents. Two SH-SY5Y NB cell lines (TB3 and TB8) expressing TrkB under the control of a tetracycline (Tet)-repressible promoter element were generated, and used to assess apoptosis resulting from treatment with cisplatin, doxorubicin, etoposide, and ***vinblastine*** . BDNF treatment of high TrkB-expressing TB8 (Tet-) and TB3 (Tet-) cells blocked drug-induced cell death in a dose-dependent manner. Only high-dose BDNF (100 ng/ml) could block the effects of chemotherapy in low TrkB-expressing cells. The ability of BDNF to rescue the cells from chemotherapeutic agent-induced cell death was inhibited by treatment with the Trk tyrosine kinase inhibitor K252a or the phosphatidylinositol 3'-kinase (PI3K) inhibitor LY294002, but not by the mitogen-activated protein kinase kinase inhibitor ***PD98059*** or the peritoneal lymphocyte gamma inhibitor U73122, indicating that both TrkB and PI3K activities are required for the survival-promoting effects of BDNF. BDNF also protected TrkB-expressing NGP and KCNR NB cells from chemotherapeutic agent-induced cell death, and LY294002 inhibited this protection. These results suggest that TrkB and BDNF can contribute to the chemoresistance of poor prognosis tumors, and that suppression of PI3K activity might improve the ability of these agents to induce the death of NB tumors.

L10 ANSWER 2 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:409696 BIOSIS
DOCUMENT NUMBER: PREV200200409696
TITLE: Activation of TrkB mediates cytoprotection against chemotherapy in neuroblastoma.
AUTHOR(S): Jaboin, Jerry Jeff (1); Van de Geijn, Gert-Jan; Kim, C. J.; Kaplan, David; Thiele, Carol J.
CORPORATE SOURCE: (1) National Cancer Institute, Bethesda, MD USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 877-878. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 3 OF 11 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002617201 MEDLINE
DOCUMENT NUMBER: 22258064 PubMed ID: 12370536
TITLE: Cerulein-induced acute pancreatitis in the rat is significantly ameliorated by treatment with MEK1/2 inhibitors U0126 and PD98059.
AUTHOR: Clemons Antoinette P; Holstein Deborah M; Galli Aurelio; Saunders Christine
CORPORATE SOURCE: Department of Biochemistry, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA.
CONTRACT NUMBER: DK-02852 (NIDDK)
SOURCE: PANCREAS, (2002 Oct) 25 (3) 251-9.
Journal code: 8608542. ISSN: 1536-4828.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021011
Last Updated on STN: 20021214
Entered Medline: 20021127
AB INTRODUCTION: Both cerulein and cholecystokinin activate mitogen-activated protein (***MAP***) ***kinase*** (ERK1/2) in vivo and in isolated pancreatic acini. AIMS AND METHODOLOGY: ERK1/2 in pancreas homogenates was activated in rats rendered pancreatitic by subcutaneous injections of cerulein (5 microg/kg per hour). To determine if blocking ERK1/2 activity might rescue cerulein-induced acute pancreatitis, the " ***MAP*** ***kinase*** ***kinase*** " (also known as MEK1/2) ***inhibitors*** ***PD98059*** and U0126 were administered in vivo. RESULTS: In rats pretreated with ***PD98059*** (10 mg/kg per i.v. injection) or U0126 (5 mg/kg per i.v. injection) 30 minutes before and then together with hourly cerulein injections for 3 hours, pancreatitis was significantly attenuated on the basis of pancreatic wet weight and histology. Serum amylase concentration was significantly reduced when ***PD98059*** was administered intraperitoneally (10 mg/kg per intraperitoneal injection). ***PD98059*** also ameliorated pancreatitis over a 6-hour cerulein time course. The phosphorylation of pancreatic ERK1/2 was attenuated in ***PD98059*** - and U0126-treated animals at both 30 minutes and 3 hours after cerulein injection. Rats rendered neutropenic with

vinblastine and pretreated with U0126 still showed attenuated manifestations of cerulein-induced acute pancreatitis, a finding suggesting that pancreatic ERK1/2 is mostly responsible for the effect, rather than infiltrating neutrophils. CONCLUSIONS: ***Inhibition*** of pancreatic ERK1/2 in vivo affords significant protection against inflammatory sequelae following cerulein-induced acute pancreatitis.

L10 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:183672 CAPLUS
DOCUMENT NUMBER: 135:265
TITLE: Inhibition of extracellular signal-regulated kinase (ERK) mediates cell cycle phase independent apoptosis in vinblastine-treated ML-1 cells
AUTHOR(S): Stadheim, Terrance A.; Xiao, Helen; Eastman, Alan
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH, 03755, USA
SOURCE: Cancer Research (2001), 61(4), 1533-1540
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Chemotherapeutic agents induce alterations in intracellular signal transduction cascades that culminate in the initiation of the apoptotic program. Here, the relationship between the mitogen-activated protein kinase (MAPK) response and apoptosis in ML-1 cells treated with vinblastine and paclitaxel was investigated. We show that these compds. elicit different effects on MAPKs with vinblastine, but not paclitaxel, increasing both c-Jun-NH2-terminal kinase (JNK) and p38 activity. However, vinblastine and paclitaxel both induced apoptosis with similar kinetics, suggesting that increased JNK and p38 activity is not required for apoptosis that is induced by microtubule interfering agents. Strikingly, the abrogation of extracellular signal-regulated kinase (ERK)-signaling by the MAPK/ERK kinase (MEK)1/2 inhibitor PD098059 in combination with vinblastine robustly induced apoptosis in ML-1 cells at a rate much faster than treatment with vinblastine alone and occurred at all phases of the cell cycle. This apoptotic induction was attributed to JNK activation because: (a) non-JNK-activating concns. of vinblastine failed to increase apoptosis in the presence of PD098059; (b) apoptosis induced by paclitaxel, which did not activate JNK, was not potentiated by PD098059; and (c) transduction of an inhibitor of JNK activity partially suppressed both JNK activity and apoptosis induced by vinblastine plus PD098059. Addnl., we found that the activation of JNK by vinblastine occurred upstream of effector caspase activation because treatment with a panspecific caspase inhibitor (valine-alanine-aspartate-fluoromethylketone) resulted in complete abrogation of apoptosis with no effect on MAPK signaling. Taken together, these data suggest that inhibition of the MEK.fwdarw.ERK signal transduction cascade alleviates cell cycle dependence for vinblastine-induced apoptosis by a mechanism that requires JNK activation.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:289938 BIOSIS
DOCUMENT NUMBER: PREV200100289938
TITLE: Norepinephrine-induced translocation of cytosolic

phospholipase A2 to the nuclear envelope via the mitogen-activated protein kinase pathway requires actin filament polymerization in rabbit vascular smooth muscle cells.

AUTHOR(S): Fatima, Soghra (1); Khandekar, Zinat (1); Malik, Kafait (1)

CORPORATE SOURCE: (1) University of Tennessee, 874 Union Avenue, Memphis, TN, 38163 USA

SOURCE: FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A542. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Cytoskeletal structures are known to be involved in the trafficking of various cellular proteins. This study was conducted to investigate the contribution of actin filaments to cytosolic phospholipase A2 (cPL >2) translocation to the nuclear envelope elicited by norepinephrine (NE) in rabbit aortic smooth muscle cells (VSMC). NE (10 muM) caused cPLA2 accumulation around the nuclear envelope as determined from its immunofluorescence. cPLA2 translocation was blocked by an ***inhibitor*** of actin filament polymerization (cytochalasin D, 15 muM) but not by colchicine (10 muM), an ***inhibitor*** of ***tubulin*** ***polymerization*** . An ***inhibitor*** of mitogen-activated protein kinase (MAPK) kinase (MEK) activity (***PD98059***) and antisense MAPK oligonucleotides (5'-AGCCGCCGCCGCCGCCGCCAT-3' 5 muM) disrupted actin filament polymerization and NE-induced cPLA2 translocation to the nuclear envelope, whereas sense and scrambled MAPK oligonucleotides (5'-ATGGCGGCGGCGGCGGCGGCT-3' 5 muM, 5'-GCACAGCCGCCTGCCGCCGCC-3' 5 muM) had no effect. These data suggest that NE-induced translocation of cPLA2 to the nuclear envelope requires intact actin filaments and that MAPK plays an important role in maintaining actin in its polymerized form and facilitating the translocation of cPLA2 to the nuclear envelope in rabbit VSMC.

L10 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:241873 CAPLUS

DOCUMENT NUMBER: 134:216717

TITLE: Microtubule interfering agents

AUTHOR(S): Watanabe, Kazushi; Kohno, Michiaki

CORPORATE SOURCE: Lab. Cell Regul., Sch. Pharm. Sci., Nagasaki Univ., Japan

SOURCE: Saishin Igaku (2001), 56(3), 390-397
CODEN: SAIGAK; ISSN: 0370-8241

PUBLISHER: Saishin Igakusha

DOCUMENT TYPE: Journal; General Review

LANGUAGE: Japanese

AB A review with 14 refs., on antitumor activities of ***microtubule*** ***interfering*** ***agents*** and its mechanism, discussing enhancement of antitumor activity (apoptosis induction) by combination of ***tubulin*** ***polymn*** . ***inhibitors*** and ***ERK*** - ***MAP*** ***kinase*** cascade blocking agents, roles of Rho and PLC.beta. in apoptosis signaling induced by ***tubulin*** ***polymn*** . ***inhibitors*** , and useful application of

microtubule ***interfering*** ***agents*** to tumor chemotherapy.

L10 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:12422 CAPLUS
DOCUMENT NUMBER: 132:216677
TITLE: Microtubule Inhibitors Elicit Differential Effects on MAP Kinase (JNK, ERK, and p38) Signaling Pathways in Human KB-3 Carcinoma Cells
AUTHOR(S): Stone, Albert A.; Chambers, Timothy C.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, AR, 72205-7199, USA
SOURCE: Experimental Cell Research (2000), 254(1), 110-119
CODEN: ECREAL; ISSN: 0014-4827
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Microtubule inhibitors are widely used in cancer chemotherapy, but the signaling mechanisms that link microtubule disarray to destructive or protective cellular responses are poorly understood. Because members of the mitogen-activated protein kinase (MAPK) family have been implicated in regulation of cell survival and cell death, the authors examd. the extent and kinetics of activation of JNK, ERK, and p38 MAPKs in response to treatment of KB-3 carcinoma cells with several microtubule inhibitors. All four agents tested (vinblastine, vincristine, Taxol, and colchicine) caused significant (6- to 13-fold) activation of JNK, concomitant inactivation of ERK, and a redn. in basal p38 MAPK activity. JNK activation and ERK inactivation occurred prior to caspase 3 activation. The microtubule inhibitors also induced phosphorylation of Raf-1 kinase. SEK-1, upstream of JNK, was also activated and phosphorylated in response to the microtubule inhibitors, and sustained phosphorylation of three endogenous JNK substrates (c-Jun, ATF-2, and JunD) was obsd. By comparison, the antitumor agent doxorubicin induced activation of JNK and p38 but had no effect on ERK activity or Raf-1. These data demonstrate that microtubule inhibitors elicit distinct and specific effects on MAPK-mediated signaling pathways and suggest in particular that coordinate and reciprocal alterations in JNK and ERK activities are important facets of the cellular response to microtubule disruption. (c) 2000 Academic Press.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 11 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999186530 MEDLINE
DOCUMENT NUMBER: 99186530 PubMed ID: 10088669
TITLE: Intracellular signals and cytoskeletal elements involved in oligodendrocyte progenitor migration.
AUTHOR: Simpson P B; Armstrong R C
CORPORATE SOURCE: Department of Anatomy and Cell Biology, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799, USA.
CONTRACT NUMBER: NS 33316 (NINDS)
SOURCE: GLIA, (1999 Mar) 26 (1) 22-35.
Journal code: 8806785. ISSN: 0894-1491.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990513

AB We have examined the potential roles of intracellular Ca2+ regulation and of multiple cytoskeletal elements in control of the directed migration of cultured oligodendrocyte progenitor cells (OPs). OPs were found to migrate in response to platelet-derived growth factor (PDGF) or to a lesser extent to basic fibroblast growth factor (FGF) in a non-additive manner. This response was ***inhibited*** by chelation of intracellular Ca2+ by using BAPTA-AM. OP migration was not evoked by the neurotransmitter agonists phenylephrine or methacholine, which elevate OP Ca2+ levels. ***Inhibition*** of the ***MAP*** ***kinase*** pathway with PD 098059 did not affect OP migration to PDGF. Within growth cone-like leading edges of migratory OP processes, monomeric and filamentous actin were found to be colocalized with myosin and filamentous actin was prominent in filopodia extending beyond the leading edge. Tubulin was distributed throughout OP processes and cell bodies. ***Inhibition*** of actin or ***tubulin*** ***polymerization*** , by using cytochalasin B or nocodazole, respectively, altered OP morphology and markedly impaired migration. ***Inhibition*** of the myosin ATPase by BDM, which prevents force-generating actin/myosin interactions, greatly ***inhibited*** the chemotaxic response at concentrations that did not disrupt cell morphology. These results indicate that growth factors stimulate OP migration by activating pathways which include intracellular Ca2+ regulation, and characterize the distribution of multiple cytoskeletal elements involved in the generation of directed OP movement.

L10 ANSWER 9 OF 11 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998442962 MEDLINE
DOCUMENT NUMBER: 98442962 PubMed ID: 9771965
TITLE: Expression of the antiapoptotic MCL1 gene product is regulated by a mitogen activated protein kinase-mediated pathway triggered through microtubule disruption and protein kinase C.
AUTHOR: Townsend K J; Trusty J L; Traupman M A; Eastman A; Craig R W
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, New Hampshire 03755-3835, USA.
CONTRACT NUMBER: CA09658 (NCI)
CA50224 (NCI)
CA57359 (NCI)
SOURCE: ONCOGENE, (1998 Sep 10) 17 (10) 1223-34.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 20000303
Entered Medline: 19981028

AB Members of both the mitogen activated protein (***MAP***)

kinase and BCL2 gene families, acting in concert with other gene products, are involved in the regulation of cell viability. However, the relationship between these families, and the signal transduction networks that control viability-regulating genes, are only beginning to be elucidated. MCL1 is a viability-promoting member of the BCL2 family that exhibits a rapid increase in expression in response to specific differentiation- and apoptosis-inducing stimuli. The signal transduction pathway involved in eliciting this increase has now been investigated. In the ML-1 human myeloblastic leukemia cell line, a rapid and sustained increase in phosphorylation of the extracellular signal-regulated kinase (ERK) members of the ***MAP*** ***kinase*** family was found to precede the increase in MCL1 expression produced by 12-O-tetradecanoylphorbol 13-acetate (TPA) or the microtubule-disrupting agents colchicine and ***vinblastine*** . ERK activation was necessary for the increase in MCL1, as ***inhibition*** of the increase in ERK phosphorylation (with the ***inhibitor*** PD 98059) prevented the increase in MCL1 expression and caused rapid cell death by apoptosis. In addition, other agents that markedly increased ERK phosphorylation (lipopolysaccharide, okadaic acid) also increased MCL1 expression. In contrast, agents that did not have this marked effect did not increase MCL1. Upstream components in this ERK-mediated pathway were also identified, where the pathway was found to be stimulated by microtubule disruption acting through protein kinase C (PKC). These results indicate that expression of the MCL1 viability-enhancing gene is regulated through a cytoskeletal disruption-induced ERK-mediated signal transduction pathway. They therefore suggest a mechanism through which the cytoskeleton and ***MAP*** ***kinases*** can exert effects on cell viability.

L10 ANSWER 10 OF 11 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97454671 MEDLINE
DOCUMENT NUMBER: 97454671 PubMed ID: 9309150
TITLE: Antimitotic agents.
AUTHOR: Fukuoka K; Saijo N
CORPORATE SOURCE: Pharmacology Division, National Cancer Center Research Institute.
SOURCE: GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1997 Sep) 24 (11) 1519-25. Ref: 22
Journal code: 7810034. ISSN: 0385-0684.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971105
Last Updated on STN: 19980206
Entered Medline: 19971017
AB Microtubules are one of the major filament of the cytoskelton and play a role in various biological functions such as mitosis, cell motility and intracellular transport. Therefore, microtubules are considered one of the most important molecular targets for cancer chemotherapy. Tubulin is one of the major microtubular components, and its polymerization and depolymerization regulate microtubular dynamics. Other microtubular components such as microtubule-associated protein (MAPs), actin, and intermediate and microfilaments have also been demonstrated to be involved

in microtubular dynamics. Recent studies provide evidence that the functions of MAPs and filaments in microtubule assembly are regulated by phosphorylation, which is catalyzed by mitogenactivated protein kinase (***MAP*** ***kinase***) and cdc2 kinase. Antimitotic agents that disrupt microtubules can be classified in two categories according to the mechanism of action, vinca alkaloids and taxanes. Vinca alkoloids, estramustine, ***rhizoxin*** , and E7010 ***inhibit*** microtubule polymerization. In contrast, taxanes such as paclitaxel and docetaxel promote polymerization of microtubules and enhance microtubule stability. We have demonstrated that paclitaxel ***inhibits*** the catalytic activity of ***MAP*** ***kinase*** and cdc2 kinase in lung cancer cell lines. This biological effect may be responsible for the increased affinity between MAP2 and tubulins, resulting in promotion of microtubule assembly. Factors that contribute to the resistance to antimitotic agents include intracellular accumulation of the drugs, genetic or functional alternations in tubulin, and alternations in ***MAP*** ***kinase*** cascade. Antimitotic agents showed a broad spectrum of preclinical antitumor activity. Clinical trials of taxanes revealed that they were effective for several cancers which were advanced or resistant against other anticancer drugs, especially for breast cancers, ovarian cancers and non-small cell lung cancers.

L10 ANSWER 11 OF 11 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 91138629 MEDLINE
DOCUMENT NUMBER: 91138629 PubMed ID: 1847331
TITLE: Activation of microtubule-associated protein kinase by microtubule disruption in quiescent rat 3Y1 cells.
AUTHOR: Shinohara-Gotoh Y; Nishida E; Hoshi M; Sakai H
CORPORATE SOURCE: Department of Biophysics and Biochemistry, Faculty of Science, University of Tokyo, Japan.
SOURCE: EXPERIMENTAL CELL RESEARCH, (1991 Mar) 193 (1) 161-6. Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 19910412
Last Updated on STN: 19980206
Entered Medline: 19910327

AB Treatment of quiescent rat fibroblastic cells (3Y1) with colchicine, a microtubule-disrupting agent, which could induce the initiation of DNA synthesis [Y. Shinohara, E. Nishida, and H. Sakai (1989) Eur. J. Biochem. 183, 275-280], activated a serine/threonine-specific protein kinase activity in cell extracts that preferentially phosphorylated exogenous microtubule-associated protein 2 (MAP2). ***Vinblastine*** treatment also activated the kinase activity, and taxol pretreatment ***inhibited*** the colchicine-induced activation of this kinase activity. The detailed biochemical characterization indicated that this microtubule disruption-activated MAP2 kinase was very similar or identical to the mitogen-activated ***MAP*** ***kinase*** in the substrate specificity and chromatographic behaviors on phosphocellulose, DEAE-cellulose, gel filtration, and phenyl-Sepharose. Pretreatment of the cells with protein synthesis ***inhibitors*** did not prevent the MAP2 kinase activation by colchicine. Moreover, phosphatase treatment inactivated the colchicine-activated MAP2 kinase activity. These data

suggest that microtubule disruption activates ***MAP*** ***kinase***
through phosphorylation.

=> d his

(FILE 'HOME' ENTERED AT 18:28:16 ON 25 FEB 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
18:28:39 ON 25 FEB 2003
L1 71 S MICROTUBULE INTERFERING AGENT
L2 2072 S (TUBULIN POLYMERIZATION) (P) INHIBIT?
L3 60255 S (DOLASTATIN 10) OR TZT-1027 ORVINCRISTINE OR VINBLASTINE OR V
L4 61971 S L1 OR L2 OR L3
L5 49667 S (ERK-MAP KINASE) OR (MAP KINASE) OR (MAP KINASE KINASE) OR (M
L6 18552 S L5 (P) INHIBIT?
L7 10056 S PD98059 OR U1026 OR PD1843522
L8 25835 S L6 OR L7
L9 28 S L4 (P) L8
L10 11 DUPLICATE REMOVE L9 (17 DUPLICATES REMOVED)

=> log y

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